

REMARKS

Claims 1 and 52 are amended. Claims 67-84 are cancelled without prejudice.

Response to Restriction Requirement

Applicants hereby make a provisional election of claims 52-66 (Group III) with traverse. It is not proper to apply any restriction requirement to claims 1-9, 11-17, and 52-66 for the reasons set forth below. Accordingly, applicants respectfully request withdrawal of the restriction requirement and substantive examination for claims 1-9, 11-17, and 52-66.

The Office action divides the claims into the following Groups:

Group I, consisting of claims 1, 5-9, and 11-17, which are drawn to a method of producing a plurality of fused cell aggregates forming a desired three dimensional structure by depositing a layer of a matrix on a substrate, embedding a plurality of cell aggregates in the layer according to a predetermined pattern so that when the cell aggregates are allowed to fuse they form the desired structure;

Group II, consisting of claims 2-4, which are drawn to the same method as recited in claim 1 and further specify a second layer of matrix is deposited on the first layer and a second plurality of cell aggregates are embedded in the second layer according to a predetermined pattern such that when the cell aggregates are allowed to fuse at least one cell aggregated embedded in the first layer is fused with at least one cell aggregate in the second layer to form the desired structure; and

Group III, consisting of claims 52-66, which are drawn to a three-dimensional layered structure comprising at least one layer of a biocompatible matrix and a plurality of cell aggregates embedded in the matrix in a predetermined pattern.

The present application is a national phase application so the restriction practice is governed by the unity of invention provisions of PCT Rule 13, 37 CFR § 1.475, and MPEP 1893.03(d). Rule 1.475(b) states in pertinent part:

"a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1) a product and a process specially adapted for the manufacture of said product . . . " (Emphasis added).

In this case claim 52 claims a product and claim 1 claims a method that includes making the product. Thus, there is unity of invention between claims 1 and 52 pursuant to Rule 1.475(b)(1).

There is also at least one common technical feature for each of claims 1-9, 11-17 and 52-66. See Rule 1.475(a). The technical contributions for the present invention include that applicants are the first to conceive of and enable production of desired three-dimensional engineered tissue structures by embedding a plurality of cell aggregates in a biocompatible matrix according to a predetermined pattern so the cell aggregates will self-assemble into the desired three-dimensional structure. The structural evolution of cells embedded in a matrix depends on several variables including, for example, the adhesive forces between cells, adhesive and cohesive forces between the cells and the matrix, the characteristics of the matrix (including its composition and spatial structure), and the pattern by which cells are arranged in the matrix. The interactions between the matrix and the cells are complex and it is very likely that structural evolution of the cells will not go as planned (i.e., the outcome will be something other than the desired structure) unless a correct combination of process variables is used. For instance, it is possible the cells could be dispersed into multiple undesired structures (e.g., as illustrated in Fig. 11B of the present application) rather than evolve into the desired structure. As is described in detail in the specification, for example, applicants developed and validated new computer modeling methods adapted to identify combinations of substances used to form the matrix, the particular types of cells and cell aggregates, and non-random embedding patterns that will reliably result in the cell aggregates evolving into the desired structure rather than an undesired structure that cannot be used for the particular application for which the tissue is being engineered.

The prior art cited in the Office action does not disclose or suggest this technical contribution. The Koibuchi article describes an experiment in which single cell aggregates are implanted into different tadpoles at various locations along a developing limb bud and the resulting morphogenesis of the limb structure is observed. Each tadpole receives only one implanted cell aggregate. See end of first paragraph of "Results" section, p. 142. The single cell aggregate is not arranged with other cell aggregates into a predetermined pattern selected to result in a desired tissue construct when the cell aggregates fuse. There is no desired structure in the experiment described in Koibuchi. The object of Koibuchi's experiment is not to produce a desired tissue construct, but to see what happens when the cell aggregate is implanted at

different locations. In particular, the objective is to determine where cells from the cell aggregate go in the developing limb in order to better understand processes controlling morphogenesis of the developing limb. Koibuchi does not explain how to embed a plurality of cell aggregates according to an embedding pattern to obtain a desired structure.

Koibuchi also reports implantation of the cell aggregate results in formation of supernumerary structures (i.e., extra digits) in the developed limb in some cases, but not others. See Page 144, left column, Table 1, and Fig. 6D. Koibuchi fails to explain why supernumerary structures result in some cases but not others. Applicants do not believe the limbs with supernumerary structures should be considered desired structures, but even if they are desired for whatever reason, Koibuchi does not explain how to use a predetermined embedding pattern for the cell aggregate to obtain the supernumerary structures. On the other hand, to the extent a normal limb is a desired structure, Koibuchi does not provide any inducement for a person having ordinary skill in the art to implant any cell aggregates into the organism at all. Instead, if the desired structure is a tadpole having a normal limb, the skilled person would simply let nature run its course without implanting any cell aggregate into the developing limb.

Libera (US 20030153078) also fails to disclose or suggest the technical contribution uniting the claims of this application. Libera discloses methods in which cells are cultured under conditions in which they arrange themselves into cell aggregates. Because the cells assemble themselves into aggregates in culture, the aggregates are not arranged in a predetermined pattern during the culturing process. The cell aggregates are harvested and then injected into diseased or degraded tissue of a living organism, using a hypodermic needle for example. There is no disclosure in Libera of injecting the cell aggregates into the tissue accordingly to any non-random predetermined pattern. Instead, as indicated in paragraphs [0017], [0030], and [0038], the process involves injecting a solution containing 100-200 cell aggregates into the defect. There is no effort to control where any particular cell aggregate is positioned at the defective tissue site relative to any other cell aggregates. Thus, Libera also fails to disclose any non-random predetermined pattern for the cell aggregates.

Because at least the technical contribution of arranging cell aggregates according to a non-random predetermined pattern is not disclosed or suggested in the prior art cited in the Office action and because each of claims 1-9, 11-17, and 52-66 includes this as a common special technical features, it is improper to issue any restriction requirement for these claims pursuant to Rule 1.475(a).

Interview Summary

Applicants thank the Examiner and his supervisor for the courtesy of the telephone interview with the undersigned on October 5, 2010. During the interview applicants discussed the basis for the finding there is no unity of invention between claims 1 and 52. In particular, applicants suggested there is unity of invention between claims 1 and 52 because Koibuchi and Libera fail to disclose at least one common technical feature - embedding a plurality of cell aggregates in a matrix according to a predetermined pattern. After considering applicants remarks, the Examiners agreed Koibuchi fails to disclose this technical feature. However, the Examiners stated, Libera could broadly be construed as disclosing a process in which a plurality of cell aggregates are embedded according to a predetermined pattern. In particular, the Examiners noted if a person determined beforehand that a random embedding pattern is what is desired, then Libera can be considered for purposes of prosecution in the Office to read on the "predetermined pattern" recitations of claims 1 and 52.

Applicants disagree with this analysis. Although the Office has a mandate to construe claims broadly during prosecution, its interpretation of the claims during prosecution must be consistent with the interpretation those skilled in the art would reach. See *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999); MPEP 2111. In this case, those skilled in the art would recognize a random pattern (e.g., as described in Libera) is not a "predetermined pattern."

The Examiners did indicate during the interview that an amendment to claims 1 and 52 explicitly excluding a random pattern (as described in Libera) from the scope of the claims would result in a finding that there is unity of invention between claims 1 and 52. After considering the matter, applicants have decided to amend the claims to recite the predetermined pattern is a non-random pattern in order to expedite substantive examination of claims 1 and 52. Support for the amendment is in at least paragraphs [0083] and [0090] of the application as filed. This amendment is without prejudice and applicants reserve the right to pursue broader patent protection through one or more continuation applications.

Remarks concerning amendments to claims 67-84

Applicants attempted to add claims 67-84 claims through a Preliminary Amendment filed August 20, 2010. However, applicants did not know about the Office action issued August 9, 2010, when they filed this Preliminary Amendment. Applicants understand the Preliminary Amendment was entered in so far as it is part of the record. The Examiner has stated to the undersigned that this Preliminary Amendment will not be considered and that this fact will be

noted in the next Office action. Applicants are not entirely sure on the basis of the facts recited above whether or not claims 67-84 are actually pending. To avoid confusion, applicants are "cancelling" these claims in this response. Applicants further plan to continue noting the status of claims 67-84 as "cancelled" in any future response and if any new claims are added to this application, applicants plan to start with claim number 85 because applicants believe this will result in the clearest record of the prosecution for this application. If the Examiner believes it would be necessary for applicants to begin numbering any new claims with number 67 to comply with the rule requiring claims to be numbered sequentially, applicants respectfully request the Examiner to provide an instruction to this effect in the next action so unnecessary delays over non-substantive issues can be avoided.

CONCLUSION

A fee transmittal including the fee for a one month extension of time is submitted herewith. The Commissioner is hereby authorized to charge any fees that are required for this response and not otherwise provided to Deposit Account No. 19-1345.

Respectfully submitted,



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